and is satisfactory for booster immunization.

4. *Critique.* The Panel found this to be an exceptionally informative submission, which brings to light the problem of whether or not the responses to "basic" immunization (i.e., 3 doses of fluid or 2 of adsorbed toxin) with recent preparations are less good than had been expected. When "full primary" immunizations (i.e., 4 doses of fluid or 3 doses of adsorbed tetanus toxoid) had been achieved, evidence of immunogenicity was satisfactory. However, this might result in 6 to 12 months of suboptimal protection.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* Tetanus toxoid is prepared from toxin produced by the method of Mueller and Miller, detoxified with formaldehyde, "refined" by the Pillemer method, diluted in sodium chloride solution, and adsorbed with not more than 0.8 mg of aluminum phosphate per does. The final concentration of toxoid is 5 Lf per dose and 0.01 percent thimerosal is present as a preservative.

2. *Labeling*—a. *Recommended use/indications.* For active immunization against tetanus, two 0.5 mL injections intramuscularly at 4 to 6 week intervals and a third dose 1 year later. The labeling notes the immunogenic superiority of adsorbed toxoids and the lack of any significant advantage of fluid toxoid as regards speed of booster response. Wound booster recommendations appear to be based on recent Public Health Service Advisory Committee on Immunization Practices recommendations.

b. *Contraindications.* Acute respiratory disease or other active infection; immunosuppressive or cytotoxic therapy.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Reports of the Investigational New Drug 262 study included in the manufacturer's submission to the Panel (Ref. 8) suggests unexpectedly poor primary responses to two preparations, one with about half the aluminum content, the other with about four times the aluminum content of the standard Lederle Laboratories Division commercial product. With the low adsorbent preparation, two of eight primary responders had subprotective levels 30 days after the dual injection. With the higher (maximum permitted) adsorbent content, two of eight primary responders again failed to reach protective levels after 2 doses.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Fourteen complaints were recorded in 4½ years during which a few million doses of adsorbed toxoid were distributed. Details are lacking but "convulsions" are mentioned in the condensed statement.

c. *Benefit/risk ratio.* The benefit-to-risk assessment would be satisfactory if the product is shown to be effective for primary immunization, and is satisfactory for booster immunization.

4. *Critique.* The Panel found this to be an exceptionally informative submission, which brings to light the problem of whether or not the responses to "basic" immunization (i.e., 3 doses of fluid or 2 or adsorbed toxoid) with recent tetanus toxoid preparations are less good than had been expected.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid, Fluid, Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This is a fluid tetanus toxoid containing 10 Lf per mL of tetanus toxoid, preserved with 1:10,000 thimerosal, and diluted in phosphate buffered saline at a pH of 7.0. The toxoiding agent is formaldehyde, and the purification process is carried out by ammonium sulfate precipitation followed by dialysis against distilled water.

The dose is not specified, for the manufacturer has not produced this material for some years, but desires to retain a license for possible future production.

2. *Labeling*—a. *Recommended use/indications.* No labeling was submitted by the manufacturer.

b. *Contraindications.* No labeling was submitted by the manufacturer.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements. In addition, the efficacy of this product in animals is well documented, due largely to a series of investigations identified in the manufacturer's submission of data to the Panel (Ref. 9) which used products from the Massachusetts Public Health Biologic Laboratories.

(2) *Human.* The efficacy of this product in humans, measured serologically, is well documented, both when used as a primary immunizing agent and when used as a tetanus booster. It appears, however, that the adsorbed tetanus toxoid from this same manufacturer induces a thirtyfold higher secondary response than does fluid toxoid, on the basis of a comparison of group geometric mean serum antitoxin titers sampled 56 days after an active-passive tetanus immunization study.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The references cited adequately document the safety of this product.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* The Panel has a general concern about the indications for use of a fluid tetanus toxoid, in the light of the documented superiority of adsorbed tetanus toxoid, not only in the magnitude but in the duration of the immune response. Furthermore, the Panel is unable to assess this product adequately in the absence of appropriate labeling, recommendations for use, and contraindications.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product has not been produced for a number of years and is not marketed in the form for which licensed and consequently there are insufficient data

on labeling, safety, and effectiveness for a contempory batch of this product.

Were appropriate labeling to be submitted, the Panel would recommend that the manufacturer retain full licensure for this product.

Tetanus Toxoid, Adsorbed Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This is an adsorbed tetanus toxoid, containing 10 Lf units per mL of tetanus toxoid, 4 mg per mL of aluminum phosphate, preserved in 1:10,000 thimerosal, and containing sodium chloride and sodium acetate as diluent. The toxoiding agent is formaldehyde, and purification is carried out by ammonium sulfate precipitation and subsequent dialysis against distilled water. The recommended dose, 0.5 mL, contains 5 Lf of tetanus toxoid.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for the routine immunization of individuals against tetanus, and for routine and emergency recall injections. For primary immunization, 2 doses of 0.5 mL are recommended at least 4 weeks apart with a reinforcing dose 6 to 12 months later and routine booster doses approximately every 10 years. It is recommended that combination toxoids with diphtheria are preferable for immunization; no mention of DPT appears in the labeling. The recommendations for use appear to be identical to those of the Public Health Service and the Advisory Committee on Immunization Practices.

b. *Contraindications.* No absolute contraindications are listed. The labeling does state that the material should not be given as elective immunization when the patient has an acute infectious illness.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements. In addition, the efficacy of this product in animals is well documented, due largely to a series of investigations identified in the manufacturer's submission of data to the Panel (Ref. 10) which used products prepared by this manufacturer.

(2) *Human.* The efficacy of this product in humans, measured serologically, is satisfactorily documented, both as regards its effectiveness as a booster and as a primary immunizing agent.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The safety of this product in humans is adequately documented.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* The manufacturer's submission contains satisfactory evidence of both safety and efficacy as well as appropriate and satisfactory labeling.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Tetanus Toxoid, Fluid, Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* This is a fluid tetanus toxoid containing 20 Lf of toxoid per mL. The toxin is prepared in a special semisynthetic culture medium which is not further described. It is also purified by methods which are not described. The diluting medium is an aqueous solution of 0.3 M glycine, and the preservative is thimerosal in a final concentration of 1:10,000.

2. *Labeling*—a. *Recommended use/indications.* The labeling states that tetanus toxoid fluid is recommended for all adults and children. Three doses of 0.5 cc (10 Lf) are injected intramuscularly or subcutaneously at an interval of 3 to 4 weeks followed by a reinforcing dose of 0.5 cc after approximately 1 year. A routine booster dose of 0.5 cc is recommended at intervals not greater than 10 years. A booster dose is also recommended immediately upon the occurrence of a wound that potentially may be contaminated unless a booster does has been given within 1 year.

The recommendation that fluid tetanus toxoid is the preferred preparation for wound booster is of dubious clinical significance. No mention of this is made in the labeling for the adsorbed product. The labeling for the fluid product could be improved by incorporating the table from the Public Health Service Advisory Committee on Immunization Practices recommendations used in the adsorbed product package insert as a convenient booster dose guide for injury.

b. *Contraindications.* Infants with a history of febrile convulsions should be given fractional doses of tetanus toxoid. Also, if unusual reaction occurs following the first injection, the volume of the second injection may have to be reduced. Any febrile respiratory illness or other active infection is reason for delaying use of tetanus toxoid, unless withholding involves greater risk.

The advice that heat-sterilized individual needles should be used as a precaution seems outdated in view of current practices. Similarly the caution in performing immunizations during polio epidemics seems unnecessary at the present time because of the rarity of such events.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data for this specific product are given. Claims for efficacy are based on references in the submission (Ref. 11) to published reports pertinent to tetanus toxoids in general.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Claims for safety include reference to literature on safety of tetanus toxoid. Data from complaint files suggest a low rate of reports of adverse reactions, especially to the adsorbed product.

c. *Benefit/risk ratio.* The benefit-to-risk assessment would be satisfactory if the product is sufficiently immunogenic in man, but because this product has not been marketed for several years, no benefit-to-risk assessment can be made.

4. *Critique.* This is a product that has not been marketed in this form for several years.

The package insert deviates from the usual U.S. recommendations for immunization, and is in need of updating.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Tetanus Toxoid Adsorbed Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* This is an adsorbed tetanus toxoid containing 20 Lf of toxid and 2.0 mg aluminum sulfate per mL. The toxin is prepared in a special semisynthetic culture medium which is not further described. It is also purified by methods which are not described. The diluting medium is an aqueous solution of 0.3 M glycine and the preservative is thimerosal in a final concentration of 1:10,000.

2. *Labeling—a. Recommended use/indications.* Tetanus toxoid adsorbed is recommended for primary immunization for tetanus. Two doses (10 Lf) are injected intramuscularly at an interval of 3 to 4 weeks followed by a reinforcing dose of 0.5 cc after approximately 1 year. A routine booster dose of 0.5 cc is recommended at intervals not greater

than 10 years. A booster dose is also recommended immediately upon the occurrence of a wound that potentially may be contaminated unless a booster dose has been given within 1 year.

b. *Contraindications.* Infants with a history of febrile convulsions should be given fractional doses of tetanus toxoid. Also, if unusual reactions occur following the first injection, the volume of the second injection may have to be reduced. Any febrile respiratory illness or other active infection is reason for delaying use of tetanus toxoid, unless withholding involves greater risk.

The advice that heat-sterilized individual needles should be used as a precaution seems outdated in view of current practice. Similarly, the caution in performing immunizations during polio epidemics seems unnecessary at the present time because of the rarity of such events.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data for this specific product were provided with the initial submission. Some additional data were provided by Merck Sharp & Dohme (Ref. 11), but were considered insufficient to demonstrate its effectiveness for primary immunization. Claims for efficacy are based on published reports pertinent to tetanus toxoids in general.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Claims for safety include reference to literature on safety of tetanus toxoid. Data from complaint files suggest a low rate of reports of adverse reactions.

c. *Benefit/risk ratio.* The benefit-to-risk assessment would be satisfactory if the product is shown to be effective for primary immunization, and is satisfactory for booster immunization.

4. *Critique.* In combination with other data available to the Bureau of Biologics about these licensed products and well-known published information on tetanus toxoid, it would seem that safety and efficacy for booster immunization are well established.

The package insert deviates from the usual U.S. recommendations for immunization, and is in need of updating.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid, Fluid, Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* This is fluid tetanus toxoid containing 4 Lf per 0.5 mL, the recommended dose. the preservative is thimerosal, 1:10,000. The culture medium employed is not specified in the material submitted; formaldehyde is used as the toxoiding agent, and subsequent purification includes ammonium sulfate precipitation and subsequent dialysis.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for primary immunization of infants and children. Three injections of 0.5 mL, 3 to 4 weeks apart are recommended, with a fourth dose approximately 1 year later and booster doses every 10 years thereafter. Booster doses with injury are recommended if more than 5 years have elapsed since the last booster. Mention is made in the labeling of the preferability of the absorbed tetanus toxoid. The recommendations for use appear to be identical to those of the Public Health Service Advisory Committee on Immunization Practices.

b. *Contraindications.* No absolute contraindications are listed. The labeling suggests that immunization be deferred during the course of any acute illness, and the elective immunization of patients over the age of 6 be deferred during an outbreak of poliomyelitis.

3. *Analysis*—a. *Efficacy—(1) Animal.* This product meets Federal requirements.

(2) *Human.* A substantial body of literature is included in the manufacturer's submission (Ref. 12) which attests to the general efficacy of tetanus toxoid. None of the evidence supplied, however, relates specifically to tetanus toxoid as produced by Merrell-National Laboratories.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The submission notes that only six reports of adverse reactions were received in a 5-year period during which many millions of doses were distributed. One of these reactions was anahylactic in nature, another was associated with upper extremely paralysis, and the other four were apparently mild reactions.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product for primary immunization cannot be established with certainty, owing to the lack of adequate evidence of efficacy. The benefit-to-risk assessment of this product is satisfactory for booster immunization.

4. *Critique.* The Panel can accept the evidence for safety of this product, as well as evidence for its efficacy in booster immunization, the latter based on the meeting of current Federal minimum requirements for efficacy in animals. Evidence supporting the efficacy of this product as a primary immunizing agent in humans, however, is lacking.

Futhermore, the Panel has some reservation about the need for fluid tetanus toxoid preparations, in the light of the documented superiority of adsorbed products, both in the terms of magnitude and duration of the immune response.

Reference to the avoidance of immunization during outbreaks of polimomyelitis are probably no longer necessary.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued.

The Panel recommends that this product be placed in Category IIIA as regards to its use in primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunizaiton. In addition, the labeling, although presently satisfactory, will require periodic revision as indicated in the Generic Statement on Labeling.

Tetanus Toxoid Adsorbed Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* This is a purified tetanus toxoid precipitated with 0.75 percent alum (aluminium potassium sulfate), in an isotonic sodium chloride solution. The toxoiding agent is formaldehyde. The purification process includes ammonium sulfate precipitation and subsequent dialysis. The final product is preserved in 1:10,000 thimerosal. The recommended dose, 0.5 mL, contains 5 Lf units of tetanus toxoid.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against tetanus in children and adults. The recommended schedule for primary immunization in both children and

adults is 2 injections 4 to 6 weeks apart, followed by a third 0.5 mL dose approximately 1 year after the second injection. A booster dose of 0.5 mL is recommended every 10 years thereafter to maintain adequate protection. If an injury other than a clean minor wound occurs more than 5 years after the last dose, a recall or booster dose is recommended. The superiority of adsorbed tetanus toxoid over fluid tetanus toxoid preparations is indicated in the labeling.

b. *Contraindications.* No absolute contraindications are listed. The labeling suggests that immunization be deferred during the course of an acute illness, and that elective immunization of patients over the age of 6 months be deferred during an outbreak of poliomyelitis.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A substantial volume of literature in the submission (Ref. 13) attests to the general efficacy of tetanus toxoid. There are no data on efficacy, however, relating specifically to tetanus toxoid produced by Merrell-National Laboratories.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The data provided are identical to those submitted for this manufacturer's fluid tetanus toxoid.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product for primary immunization cannot be precisely estimated, owing to the lack of data supporting the efficacy of this product when used as a primary immunizing agent. The benefit-to-risk assessment of this product for booster immunization is satisfactory.

4. *Critique.* The Panel accepts the evidence for the safety of this product, as well as evidence supporting its efficacy for booster immunization, the latter based on meeting current Federal minimum requirements in animal tests. Specific data in support of the efficacy of this product in humans when used as a primary immunizing agent are lacking.

References to the avoidance of immunization during outbreaks of poliomyelitis are probably no longer necessary.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued.

The Panel recommends that this product be placed in Category IIIA as regards its use in primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. In addition, the labeling, although presently satisfactory, will require periodic revision as indicated in the Generic Statement on Labeling.

Tetanus Toxoid, Fluid, Manufactured by Parke, Davis & Co.

1. *Description.* This toxid contains 5 Lf tetanus toxid refined by ultrafiltration per 0.5 mL dose with 0.01 percent thimerosal as preservative.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against tetanus. The labeling notes that the American Academy of Pediatrics and the Public Health Service Advisory Committee on Immunization Practices recommended use of adsorbed rather than fluid toxoid (but, nevertheless, the labeling recommends this fluid toxoid). Contrary to general practice, it recommends the use of fluid toxoid with TIG. It fails to note the usual precautions about the reduced efficacy in immunosuppressed individuals.

b. *Contraindications.* Acute febrile illness is a contraindication. The usual precautions regarding steril equipment, availability of epinephrine, and avoidance of injection into blood vessels are mentioned.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data are presented for this specific product. Some published data (Ref. 13) suggest that the primary immune response to a virtually identical, but experimental, fluid preparation is rather short-lived. No data are provided on response after reinforcing inoculation.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The large number of doses distributed, and the very small number of complaints received, together with the apparently satisfactory experience of MacLennan (Ref. 13), suggest that this product is safe in man.

c. *Benefit/risk ratio.* There is some reason to question the benefit gained from use of this fluid product, in light of the limited available data on efficacy for primary immunization. The benefit-to-risk assessment for this product when used for booster immunization is satisfactory.

4. *Critique.* The labeling needs careful revision and updating as noted above. The lack of a buffer in this product is surprising. Available data are insufficient to classify this product when used for primary immunization.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this prodict be placed in Category IIIA as regards its use for primary immunization and that the apprpriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Parke, Davis & Co.

1. *Description.* Contains 5 Lf tetanus toxid refined by ultrafiltration per 0.5 mL dose with 0.01 percent thimerosal as preservative. The toxoid is adsorbed on 2.5 mg aluminum phosphate per dose.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against tetanus.

b. *Contraindications.* Acute febrile illness; standard precautions regarding sterile equipment, availability of epinephrine, and avoidance of intravenous injection are mentioned. The possible reduced efficacy of the product in immunosuppressed individuals is not mentioned.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data were presented for this specific product. Published studies on a similar experimental product (Ref. 13) indicate a good immune response in man, but later studies on a different group (Ref. 14) showed an unexpectedly poor response to the first 2 doses.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The large number of doses distributed, and the very small number of complaints received, together with the apparently satisfactory experience of MacLennan (Ref. 13), suggest that this product is safe in man.

c. *Benefit/risk ratio.* Provided the efficacy of this preparation for primary immunization is clearly established, the benefit-to-risk assessment would be satisfactory and is satisfactory for booster immunization.

4. *Critique.* This is one of the few currently used tetanus toxoids for which even limited data for primary

immunization in man are available. Six out of six patients have shown a vigorous primary response by hemagglutinations titer to 2 doses. However, the data are less than required. Hence, further evaluation in man is necessary in order to achieve statistical significance. Post-exposure booster recommendations are now obsolete. The labeling needs some expansion, revision, and updating.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exeed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid Adsorbed Manufactured by Swiss Serum and Vaccine Institute Berne

1. *Description.* This is an aluminum phosphate adsorbed preparation of tetanus toxoid containing 20 Lf per mL. It contains aluminum phosphate, 2 mg per mL, and is preserved with 0.01 percent thimerosal. The product is said to be purified, but neither the method of purification nor detoxification is described.

2. *Labeling*—a. *Recommended use/indications.* The product is recommended for active immunization against tetanus. The recommended schedule consists of 2 injections of 0.5 mL each at an interval of 4 weeks and a third injection of 0.5 mL 6 to 12 months later. Booster doses are recommended every 10 years, or in the case of injury, provided the patient has not had an injection within the previous year.

b. *Contraindications.* This product should not be given during acute illnesses. This product should be administered to children with a history of convulsions only under medical supervision.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Several published studies are cited in the manufacturer's submission to the Panel (Ref. 15) which show that the product induces an adequate antitoxin response when given as a booster. The data show that these responses are satisfactory when given simultaneously with tetanus immune globulin. The data do not clearly demonstrate the efficacy of the product as a primary immunizing agent.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Reaction rates given for an industrial population studied are low and within expected limits.

c. *Benefit/risk ratio.* Assuming that the product is found to be an effective primary immunizing agent, the benefit-to-risk assessment would be satisfactory and is satisfactory for booster immunization.

d. *Labeling.* This package insert is in need of revision to bring it up-to-date with current recommendations. A booster dose is recommended in the case of injury if more than 1 year has elapsed since the last injection. This obsolete recommendation invites excessive booster doses; the latest Public Health Service Advisory Committee on Immunization Practices recommendations should be incorporated to clarify this problem and the related need to use tetanus immune globulin in some patients.

The statement concerning administration of the product to children prone to convulsions only "under medical supervision" seems superfluous. The product should always be so administered.

4. *Critique.* This product has been demonstrated to be adequate for booster immunization. Adequate data are not available to demonstrate its efficacy as a primary immunizing agent.

The safety of the product has been adequately demonstrated, and no unusual frequency of untoward local reactions have been noted.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus Toxoid, Fluid, Manufactured by Texas Department of Health Resources

1. *Description.* This is a fluid tetanus toxoid prepared by detoxification of tetanus toxin with formaldehyde (and "heat"), purified by ammonium sulfate fractionation, diluted to 40 Lf per dose, and preserved with 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against tetanus. The basic immunization schedule consists of three 1 mL doses at 3 to 4 week intervals with a fourth dose 1 year later. Routine boosters are recommended at 5-year intervals.

b. *Contraindications.* None listed.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No human data on antitoxin response to primary or booster immunization are presented. "Periodic blood antitoxin" levels are mentioned but no data were provided. A chart labeled "Tetanus Mortality and Immunization in Texas" (Ref. 16) submitted as evidence of efficacy is unsatisfactory and could be interpreted as suggesting that the decline in incidence slowed down with the introduction of toxoid.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No controlled studies of reaction rates have been performed. It is stated that no adverse reactions were reported in the past 10 years. The high Lf content of this product is a matter of some concern in this regard.

c. *Benefit/risk ratio.* Assuming that evidence can be presented that the product is effective for primary immunization, the benefit-to-risk assessment would be satisfactory, and is satisfactory for booster immunization.

d. *Labeling.* The package insert is in need of professional review and revision to bring it up-to-date with current recommendations. For exposure to risk of tetanus, a booster is recommended if a year has elapsed since the last injection. This obsolete recommendation invites excessive boosters; the latest Public Health Service Advisory Committee on Immunization Practices recommendations should be incorporated to clarify this problem and the related need to use tetanus immune globulin in certain patients. The labeling should put special emphasis on the need for the reinforcing dose at 1 year. Since this is a fluid product, the labeling should also note the published evidence questioning the advisability of using fluid toxoid simultaneously with